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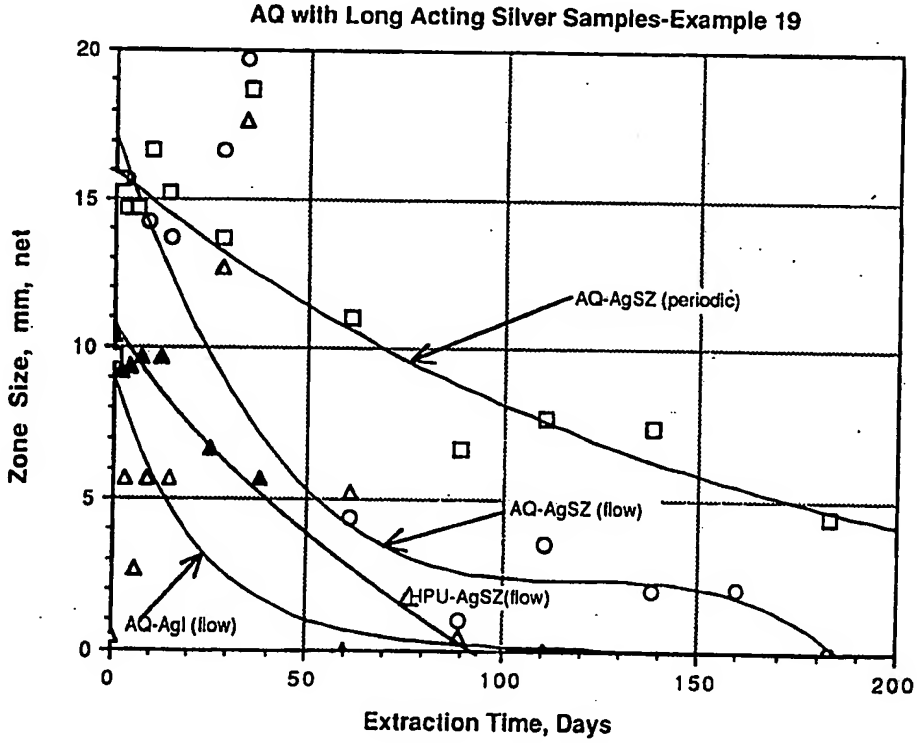
(54) Title: THERAPEUTIC AGENT IN HYDROPHILIC MATRIX

(57) Abstract

A chemical is incorporated in a swellable hydrophilic matrix. The chemical or a precursor dissolved can be dissolved in a solution having a solvent which swells the matrix by at least 10 %. The chemical is then deposited in the matrix in a form in which it exhibits a relatively low aqueous solution solubility. The resulting product exhibits long term emission of the chemical in its neighborhood for medical and other purposes. The product may be, for example, a cannula.



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Description

Therapeutic Agent In Hydrophilic Matrix

Field of Invention

The invention relates to the provision of chemicals such as therapeutic agents dispersed in hydrophilic media. Such media are useful for time release of the chemicals.

Background of the Invention

Many methods are known for providing active ingredients at or on the surfaces of articles. More specifically, various methods have been employed to provide antibacterial or anticoagulation substances on the surfaces of medical devices. Such methods include simple surface coating of the device, covalent attachment of active ingredients to the surfaces of the devices and incorporation of the desired material throughout the bulk of the devices, among others. Also, various coatings or layers are often applied to the article and these coatings can then be treated to contain an active medicament. It is desired that these incorporated medicaments accumulate on or migrate to the surface to provide their effect. One use is for drug delivery whereby the medicament on the surface can leach into the surrounding organism and provide a clinically useful effect. Another use is to provide an implanted device (such as a catheter) with sufficient antibacterial medicament on the surface to inhibit bacterial colonization of the implant and prolong its useful life. Similarly, an anticoagulant medication can be used to avoid blood clotting, fibrin accumulation or blood activation.

It would be desirable if one could provide an article with a chemical dispersed throughout the article and to be able to provide it in such a manner that the rate of diffusion out of the article could be selected for a specific end use. For example, if a medical device is to be implanted for only one or two months it would be desirable to be able to provide such a device with only the minimum necessary amount of medicament, since excessive release of such medicaments can create unwanted systemic side effects, and to be able to control the rate of release of the medicament so that an effective amount is present over the entire period of implantation. If the device is to be implanted for a longer period of time, e.g., for a year or more, a higher amount of medicament could be provided and the rate of leaching could be controlled so that an effective amount of the medicament would be present for the longer period of time. It would also be desirable to be able to do this with medicaments which, like many medicaments, are only stable under relatively mild conditions and which would, therefore, be deleteriously affected if subjected to harsh conditions during incorporation into or onto the surface of a device. Still further, it would be desirable to provide implantable medical devices such as urinary, venous, drainage, perfusion and dialysis catheters which can be protected from harboring infectious organisms such as those already present on the patient's skin or in the blood or urine. Unfortunately, prior art methods, as discussed in following, have not been capable of providing such design flexibility.

Kahn, et al in U.S. Patent 4,925,668 discloses a method of incorporating chlorhexidine in the bulk of slightly hydrophilic polymers by melt processing during formation of the article followed by extrusion and then by dip coating with a solution of

chlorhexidine and silicone. This method has very limited applicability because very few desirable active ingredients are able to survive the aggressive temperatures, pressures and shear conditions in the extrusion melt process.

Kohn, et al in U.S. Patent 4,806,621 discloses a method similar to that of Kahn, et al for providing medicaments and the like dispersed in a hydrophobic poly(iminocarbonate) polymeric matrix. As with the Kahn, et al procedure, very few desirable active ingredients are able to survive the aggressive temperatures, pressures and shear conditions in processing. Also, the resulting product biodegrades which can be a detriment when one desires a long term implant which is to eventually be removed. Further, since the polymer is hydrophobic it cannot, in at least most instances, soften and/or swell as may be desirable if it is used as, for example, a cannula.

Mochizuki, et al in U.S. Patent 4,675,347 discloses the incorporation of cationic antimicrobial agents such as chlorhexidine into cationic natural rubbers to provide long term drug delivery from the resulting hydrophobic polymers. As with the Kahn, et al procedure, very few desirable active ingredients are able to survive the aggressive temperatures, pressures and shear conditions in processing. Further, since the polymer is hydrophobic it cannot, in at least most instances, soften and/or swell as may be desirable if it is used as, for example, a cannula.

Fox, et al in U.S. Patent 4,581,028 discuss a method which provides an implantable hydrophobic device with an antimicrobial metal sulfonamide salt. These salts are basically coated on the surface of the article. Example 3 of this patent discloses an in situ technique for forming silver sulfadiazine ("AgSZ") on or just into the polymer surface. The antibiotic content of such materials is confined to

the surface layer. Table IV of Fox, et al shows 33 to 50% of the active ingredient was washed off within one day by simple soaking. Thus, these silver salts using this method of association on relatively hydrophobic polyurethane or silicone tubing as disclosed have antibacterial effectiveness only for extremely short times. The term "relatively" is used with respect to the tubing since these polyurethanes have some hydrophilic character in that they will absorb about 1% water but are clearly not hydrophilic in the sense defined herein in that they absorb much less than 10% water. Other Fox, et al patents of interest include U.S. Patents 4,535,078, 4,612,337 and 4,563,485.

Japanese patent publication JP 6036064 discusses formation of nearly insoluble chlorhexidine derivatives by soaking hydrophobic rubber, polyurethane, silicone or PVC in a chlorhexidine solution to provide polymers with chlorhexidine deposited on their surfaces then treating the polymers with acid to insolubilize the chlorhexidine. However, even the most effective example given had activity against bacillus subtilis for only thirty two days.

Other prior art of interest includes U.S. Patent 4,994,047, issued February 19, 1991 to J. M. Walker and J. R. Thomas, and U.S. Patent 4,883,699, issued November 28, 1989, each of which generally mentions that water soluble or water dispersible medicaments may be included in hydrophilic catheters. These patents are not, however, concerned with the method of incorporation of the medicaments in the catheters.

The capability of incorporating a wide range of chemicals, particularly medicaments, in hydrophilic and preferably swellable and softenable polymeric matrixes would be particularly desirable. Also desirable is the ability to control the length of time such medicaments will continue to leach out of such

matrixes. Still further, it would be desirable to be able to provide particularly long effective periods for hydrophilic matrixes which contained a slow release medicament. Also, it would be desirable to be able to incorporate a medicament in a preformed medical device in that the device could be formed by procedures which would destroy or deleteriously effect the medicament.

The present invention is directed to overcoming one or more of the problems set forth above.

Summary of Invention

In accordance with an embodiment of the invention a method is set forth of incorporating a chemical in a swellable hydrophilic matrix. The method comprises contacting the matrix with a solution having the chemical or a precursor of the chemical dissolved therein, the solution including a solvent which is selected to swell the matrix by at least 10% in volume and sufficient of the precursor or of the chemical to provide a desired level of the precursor or of the chemical dispersed throughout the matrix. Thereafter the chemical is deposited in the matrix in a form in which it exhibits a selectable aqueous solution solubility.

In accordance with another embodiment of the invention a method is set forth of incorporating a medicament in a preformed medical device comprising a swellable hydrophilic matrix. The method comprises contacting the matrix with a solution having the medicament or a precursor of the medicament dissolved therein, the solution including a solvent which is selected to swell the matrix by at least 10% in volume and sufficient of the precursor or of the medicament to provide a desired level of the precursor or of the medicament dispersed throughout the matrix.

Thereafter the medicament is deposited into the matrix in a form in which it exhibits a selectable aqueous solution solubility in such a manner that it has therapeutic effectiveness only in a narrow zone around the matrix but the effectiveness lasts for an extended period of time.

Yet another embodiment of the invention is a method of incorporating a medicament which is substantially insoluble in water in a preformed medical device comprising a swellable hydrophilic matrix. The method comprises contacting the matrix with a solution having the medicament dissolved therein, the solution including a solvent which includes a non-aqueous component and is selected to swell the matrix by at least 10% in volume, the solution further including sufficient of the medicament to provide a desired level of the medicament dispersed throughout the matrix. Thereafter the non-aqueous component is removed and the medicament is thereby deposited into the matrix.

Another embodiment yet of the invention is a method of providing a preformed medical device which comprises a swellable hydrophilic matrix with long lasting antibiotic effectiveness. The method comprises absorbing chlorhexidine acetate into the matrix.

Still another embodiment of the invention is a medical device comprising a swellable hydrophilic matrix which swells at least 10% in volume on immersion in water and which has uniformly dispersed throughout a substantially water insoluble medicament and being characterized in that the medicament is dispersed in the matrix in such a manner that it exhibits therapeutic effectiveness for at least 5 days.

Articles and devices of the invention have applications in many fields including gradual

diffusion of substances to inhibit surface corrosion or biofouling on surfaces such as polymer liners for boiler tubes or the membranes in oxygenators, slow medicament release to deliver therapeutic medicament doses locally (in a narrow zone about the articles or devices) and continued delivery of antibiotics from the bulk to the surface to prevent or retard bacterial growth and infection on medical devices for long periods of time. Hydrophilic matrixes loaded in accordance with the present invention can release chemicals over very long periods of time due to the bulk dispersion of the chemical throughout the matrix and due to the fact that the substantially insoluble (really very slightly soluble in aqueous media, i.e., in the intended use environment, e.g., in blood, urine or other body fluids) or second form of the chemical can be selected to have very low solubility. Or, at the designers choice, the chemical may be selected so that it is dispersed within a selectable time period by selection of a second form for the chemical which is sufficiently soluble so that it will be substantially completely exuded in the selected time period.

Brief Description Of The Drawings

The invention will be better understood by reference to the figures of the drawings, wherein:

Figure 1 is a graphical representation of the experimental data of Examples 19A, 19B, 19C and 19D and demonstrates the bactericidal effectiveness of relatively insoluble silver compounds over extended testing periods;

Figure 2 is a graphical representation of the testing of the catheter tubing of Examples 6B, 6E, 6F and 6H as tested in accordance with Example 22 and demonstrating that the duration of bactericidal

effectiveness may be varied by the choice of the hydrophilic swelling substrate or by the form of the drug which is selected;

Figure 3 is a graphical representation of the testing of the catheter tubing of Example 4 demonstrating the dependance of bactericidal effectiveness on the relative solubility and amount of the bactericide;

Figure 4 is a graphical representation of the testing of the catheter tubing of Example 4 demonstrating the dependance of bactericidal effectiveness on the relative solubility and amount of the bactericide; and

Figure 5 is a graphical representation of the testing of the catheter tubing of Example 7 as tested according to Example 23 and demonstrating long term bactericidal effectiveness.

Best Mode For Carrying Out Invention

While the following discussion will center on the medical aspects of the invention, such focus is not meant to be limiting and other uses of the invention are also contemplated as falling within its scope.

This invention relates primarily to methods for incorporation of chemicals such as medicaments inside (as well as on the surface) of hydrophilic water swellable materials. Specifically various chemical techniques are disclosed whereby sparingly soluble (i.e. nearly insoluble) drugs can be incorporated and disbursed throughout the bulk of water swellable polymeric materials. Such materials can be made into useful devices which, when exposed to aqueous solutions, will gradually release the incorporated medicament over long periods of time.

The term hydrophilic is well understood in the art but is generally used in a relative sense.

This term is used in a more rigorously defined sense when used in describing the present invention. In particular, a matrix which is defined as water swellable and hydrophilic in accordance with the present invention must have the property of being capable of absorbing water and swelling at least 10%, more preferably at least 20% and still more preferably at least 50% in volume when soaked in an aqueous solution. While being water swellable, the matrix is not water soluble, at least at use temperature (about 37°C. in the case of medical devices).

The hydrophilic matrixes or materials useful in the practice of the invention, when used for pharmaceutical purposes, can be of any material suitable for introduction into a living subject. Preferably, these materials are polymeric in nature and, when used as cannulae, are selected to be sufficiently stiff for insertion. Even more preferred are those compositions which soften or exhibit a decreased 2.5% Secant Modulus upon, for example, exposure to liquids, insertion of the distal end portion of the cannula into the body of a living subject and its maintenance therein. Particularly, preferred compositions absorb liquid (i.e., hydrate) and thereafter soften to a 2.5% Secant Modulus of less than 7,000 N/cm^2 which reduces the trauma to the surrounding tissues of the subject. The term softening ratio is used herein to refer to the ratio of the 2.5% Secant Modulus values of the composition selected in the form of a tubular cannula initially to the 2.5% Secant Modulus of the composition when softened (from dry matrix at 20°C. to wet matrix at 37°C.). The overall matrix must have the ability to hydrate sufficiently to absorb sufficient water to swell at least 10% in volume, as previously stated. It is preferred that the composition soften with a softening ratio of at least about 5:1, more preferably

at least about 10:1 and still more preferably at least about 20:1, when it is to be used as a cannula.

Examples of softening polymers useful in the practice of the invention are those described in U. S. Patents Nos.4,883,699, issued November 28, 1987 and 4,911,691, issued March 27, 1990, both of which are incorporated herein by reference. The preferred composition for the matrix comprises:

(a) a first phase which comprises a substantially non-hydrophilic polymeric component; and

(b) a second phase which comprises a hydrophilic polymeric component;

the material (i) being capable of absorbing water to an extent that its softens with a softening ratio of at least about 5:1 and/or swells with a swelling ratio of at least about 1.1:1; and (ii) when substantially completely hydrated, having an energy to break of at least about 700 N-cm/cm^3 and a 2.5% Secant Modulus of less than about 7,000 N/cm^2. For convenience such materials are referred to herein by the designation "AQ".

Also useful are swelling and softening hydrophilic polyurethane (HPU) polymers such as those described in U.S. Patents Nos. 4,359,558; 4,424,305; 4,454,309 and 4,439,583 assigned to Tyndale Plains-Hunter Ltd. and in Canadian Patent 2,017,951 assigned to Becton, Dickenson and Company and block hydrolyzed polyacrylonitrile (PAN) polymers described in U.S. Patents 4,123,406 and 4,480,642, each of which is incorporated herein by reference. Indeed, any hydrophilic swellable polymers which can be formulated into devices, which are compatible with the specific medicament or chemical which is to be dispersed in them and which are compatible with their use environment, can be used in practicing the invention.

More specifically the present invention relates to depositing sparingly soluble substances

inside the bulk material by in situ chemical techniques. The desired chemical or a precursor of that chemical in a soluble form, is absorbed or imbibed inside the bulk of the hydrophilic water swellable polymeric material. Once the precursor or the chemical is absorbed or imbibed the chemical is deposited within the material. In many instances this can be done by converting the precursor into the chemical which is usually much less soluble, but is efficacious for its intended purpose. Such a transformation can be accomplished by any of many well known methods. Examples of some of these types of processes are precipitation with metal salts; formation of "insoluble" salt complexes (salinification); insolubilization by pH change; changing a polar drug precursor, in situ, into a non-polar active medicament (generally using a polar aprotic solvent) and acid base precipitation.

For example, soluble acidic or basic medicaments, or their precursors which may or may not have the same medicament properties, can be changed in situ to less soluble (or more soluble, if desired) derivatives by reaction with metal ions or acid salts. Examples of acidic drugs include sulfonamides (sulfadiazine), nalidixic acid derivatives, cephalosporins and various penicillins. These can be precipitated out of solution in situ by calcium, zinc, silver or other metal ions. In short, an acidic medicament (e.g., RCOOH) can be precipitated by either polyvalent metal ions or by fatty cations (alkyl quaternary amines, amidines and guanidines). For example, such compounds as myristyltrimethylammonium bromide, stearyltrimethylammonium chloride and the like, can be used to make salts of medicaments with carboxylic acid functions. In the case of fatty cations the use of polar organic solvents (with or without water) may be desirable. Examples of basic

medicaments include antiseptics (chlorhexidine, benzalkonium chloride) and polypeptides (polymyxin). These can be precipitated out of solution in situ, for example, by reaction with fatty acids. For example, such compounds as sodium dodecylsulfate, sodium stearyl sulfate and the like can be used to make salts of medicaments having amine functionality. This technique can also be used with fatty alcohol mono sulfate esters which form strong salts with amines. Phospho-diglycerides can be used as the precipitating acid with the aid of organic solvents. Many medicaments are amphoteric in that they have groups which can exhibit acidic or basic functionality and their solubilities can be altered by suitable acidic or basic reagents. In some cases it is possible by changing pH to alter the solubility of various medicaments in situ. Tetracyclines (doxycycline, chlorteracycline), sulfonamides (sulfaguanidine, sulfapyridine), nitrofurantoins and other medicaments can be precipitated in situ by use of an appropriate acid or base. Nearly insoluble derivatives can be selected to diffuse out at different rates depending on the eluting environment. For vascular or urinary applications, with pH values of about 7.4 and 5.5 respectively, it is an advantage to be able to design the in situ deposited medicament to elute out at a desired rate at the specific pH of use of the device.

The substances formed inside the material by this "in situ" process can be selected to have desired solubility and activity. More soluble materials will diffuse out more quickly and in larger quantities. Insoluble (really very slightly soluble) materials will remain effectively permanently dispersed in the material. This could be useful for certain anticoagulants, antifouling agents, antibiotics, or radiopacifiers, for example. Or more preferably, the formed substance, if slightly soluble, can elute at a

designated rate sufficient to provide antibiotic activity at the surface for long periods of time. The formed medicament can be chosen for activity against various types of organisms and/or for duration of effect. The form of the substance can often be controlled so that it will have a desired solubility. If the substance is, for example, silver, it can be deposited as the chloride, the bromide, the iodide, the sulfadiazine, etc., salt, all of which have different solubilities.

Any medicament which is compatible with a human or animal body and which can be changed in solubility and/or formed in situ in a hydrophilic water swellable matrix can be used in the method of the present invention. Representative antimicrobial agents include norfloxacin, oxacillin, nafcillin, sulfadiazine, pefloxacin, tobramycin, piromidic acid, pipemidic acid, enoxacin, AM-833, and cephalosporins, such as cefmenoxime, moxalactam, cefazolin, cefamandole, etc. Note that this is but a representative listing and the invention is not contemplated as being in any way limited to the use of these specific medicaments. Furthermore, agents which are not antimicrobial but which have other desirable properties are also useful medicaments and fall within the scope of the term medicament as used herein. Such other medicaments include anticoagulants, such as heparin, urokinase, antifouling agents, etc.

By forming the substance inside the polymer article much longer lasting activity can be obtained compared to surface treatments as disclosed in the prior art. The bulk of the water swellable material acts as a slowly releasing reservoir and it can accumulate a large amount of active ingredient.

Another method of depositing a substantially water insoluble substance in a hydrophilic water swellable matrix is by swelling the matrix with a

solution of the substance in a non-aqueous or mixed aqueous/non-aqueous solvent system with the non-aqueous component being readily removable, for example readily volatilizable, and being, for example, methanol, ethanol, formamide, acetone, tetrahydrofuran, dimethyl formamide, dimethylacetamide, methylene chloride, ethyl acetate 1-methyl-2-pyrolidinone, dimethylsulfoxide, sulfolane, methyl ethyl ketone, γ-butyrolactone, diethylcarbonate, ethylene carbonate or the like and mixtures thereof with each other and/or with water. The solvent system must be chosen so as to provide a desired level of the medicament and so that the matrix will absorb or imbibe sufficient of the solvent system so as to provide the desired amount of the medicament. Generally the matrix and solvent system must be such that the matrix absorbs or imbibes sufficient of the solvent system so that the matrix swells by at least 10%, more preferably at least 20% and still more preferably at least 50% in volume. By readily volatilizable is meant that the solvent system can be volatilized at a temperature and in a manner that will not deleteriously affect the medicament being deposited or the matrix. Other removing techniques such as solvent extraction/exchange may also be used so long as they will not deleteriously affect the medicament being deposited or the matrix. Certain medicaments can be selected that are soluble in these solvent systems and are nearly insoluble in water.

The polymeric materials are water or aqueous solution swellable. If the polymer is not water swellable, then effective rates of incorporated (by whichever method) and of medicament release will only be obtained in special circumstances. This in situ method can also be applied to pure soft formless hydrogels but the products can just as easily be mixed into such hydrogels under mild conditions with few

complications. The preferred polymeric materials are water swellable compositions which are formed into useful articles and medical devices. Products from these polymeric materials can be made to have long lasting antibiotic activity by using the described in situ drug formation process.

In most instances the water which has swollen the polymer during or following the deposition of the substance in the polymer matrix will be removed with the matrix shrinking in size. This is the case when the matrix is in the nature of a cannula which should initially be stiff so it can be inserted in a patient and will then soften and swell following such insertion. In other instances it may not be necessary or desirable to remover the water. For example, a nerve sheath would preferably be swelled and relatively soft when inserted about an injured nerve or nerve connection.

Articles having such long lasting time release of medicament properties have significant advantages compared to articles made by the current state of the art. Incorporation of the medicament throughout the bulk of the article provides a much larger reservoir of medicament compared to incorporating the medicament only on or slightly inside the surface (layers) of the present art. This bulk reservoir results in diffusion and release of the active ingredient for substantially longer periods of time than surface coatings.

Furthermore, if only a local but long lasting effect, as opposed to a systemic effect, is desired a relatively low concentration of a low solubility medicament can be provided throughout the bulk of the article and, due to the low concentration and low solubility, this effect will be local and will endure for a long period of time. Thus, therapeutic effectiveness can be provided for an extended period

of time, for example, 5 days or more, preferably 10 days or more and still more preferably 30 days or more, in a narrow region, for example, within 50 mm, preferably within 25 mm, of a medicament containing medical device.

Especially preferred are tubular articles which include a medicament impervious layer along with a hydrophilic layer from which the medicament can elute. The medicament impervious layer in such articles prevents the medicament from diffusing past it away from the hydrophilic layer. In this manner diffusion can de controlled so as to occur only in a desired direction. Coextruded layered tubing such as that described in U.S. Patent 4,994,047, which is incorporated herein by reference, with the hydrophilic layer having an in situ deposited medicament as described herein, are the preferred articles. The impervious layer can be a middle layer between two different hydrophilic layers each of which has a different medicament dispersed in it whereby different medicaments will diffuse in different directions. Such can be desirable, for example, when the tubing is in the nature of a cannula. An inner hydrophilic layer can provide a selected medicament to the blood or other fluid passing through the cannula while an outer hydrophilic layer, separated from the inner hydrophilic layer by a medicament impervious layer, can provide a different selected medicament to the tissue, for example, to minimize irritation. Also, a hydrophilic medicament containing matrix may be coated, by solution or other process, to provide a medicament impervious coating on one or more selected areas where introduction of the medicament is not desired.

In situ chemical or physical incorporation of, for example, medicaments, in accordance with the invention can take place in a finished article or

device. This is an advantage because the number of useful medicaments, etc. that can survive the high temperatures, shear and other processing conditions required to form polymeric articles is severely limited. The present invention can also be performed on complex shaped articles or on selected portions of finished articles. See, for example, U.S. Patent 4,925,668 which is incorporated herein by reference. As the examples below show, the present invention avoids the problems associated with incorporating medicaments during polymer processing, provides a method of incorporating "insoluble" medicaments throughout the bulk of the material, and produces long lasting slow release of the incorporated medicaments.

The following examples show the benefit of the present in situ technique for different types of in situ drug formation and show extended, effective drug release. Some examples from the teachings of the prior are given for comparative purposes.

It will be obvious to those skilled in the art that this in situ technique may be combined with existing methods, or that it may be used to provide more than one type of nearly insoluble drug, or that different drugs may be incorporated into different parts of a device, etc.

Examples 1-7

Preparation of Materials

Example 1 Water Soluble Antibiotic: Gentamicin Sulfate

1A. Melt Processed Into Article. The prior art elastomer hydrogel composition AQ was formulated into tubing samples as described in U.S. Patents 4,883,699 and 4,840,622, the latter of which is incorporated herein by

reference. An extrusion process was used rather than a milling process. The composition contained 1.5 wt% gentamicin sulfate (Sigma Chemical Co. 565 µg/mg, 8.2% H_2O) and was melt extruded into catheter tubing. Although gentamicin sulfate has a melting point (218-237°C.) significantly higher (about 50°C.) than the melt and extrusion temperatures used, the melt extruded tubing processed with difficulty and had a commercially unacceptable lumpy surface and amber tan color. The tubing was subsequently crosslinked by radiation.

1B. Soaked into article. 2-3 cm sections of crosslinked elastomer hydrogel AQ tubing, made as in Example 1A but without the gentamicin sulfate, were immersed in 50 mg/ml gentamicin sulfate solution (Sigma Chemical Co.). After 5 hours fresh solution was added for 14 additional hours. The tubing segments were rinsed with water, blotted on paper towels, then air dried. The tubing was exposed to an additional 2.5 megarads of radiation. This crosslinked elastomer hydrogel material showed a volume swell or expansion of about 120% after immersion in aqueous solutions for several hours. These samples were calculated to contain about 5 wt.% gentamicin sulfate. The calculation was made by noting the volume of swelling, which was equated to the amount of solution absorbed. It was assumed that after evaporation of the solution all of the medicament remained in the tubing. Such

calculations were made for all swelling samples in the examples in this specification.

Example 2 Metal Salt Derivative: Silver Sulfadiazine

2A. Sodium Sulfadiazine Several approximately three feet long pieces of crosslinked elastomeric hydrogel AQ tubing were threaded into a larger polyethylene (PE) tube. The PE tube was bent into a U shape and 4°C. water was added, immersing all but the ends of the elastomer hydrogel tubing (so that solution could not by accident be trapped within the tubing). All materials were maintained at 4°C. throughout the experiment. After two hours the tubing was rinsed with and reimmersed in cold water for two additional hours. Cold sodium sulfadiazine (NaSZ) (Biochemical Industries, Inc.; USP grade) solution, 0.082 molar, was then added and after two hours, the tubing was rinsed and reimmersed in fresh NaSZ solution. After two hours, the samples were removed from the cold, rinsed with water, soaked for 3 min in pH 7.4 phosphate buffered saline (PBS), rinsed again with water and blotted dry. The resulting tubing was calculated to contain about 2.2 wt% NaSZ.

2B. Control tubing One strand of tubing was removed from the strands of tubing from Example 2A before the addition of the NaSZ solution. It was handled in a similar way as the tubing described in 2A, except water was used in place of medicament solution.

Similar control tubing samples were used in all antibiotic testing described in the examples herein. In each instance identically handled control tubing samples were run along side all various medicament samples. Control tubing, extracted for various times, was used as part of each microbiological assay sample set. The control samples invariably showed no inhibition activity or destruction of bacteria, i.e., a zero bacteria free zone size, as defined hereinbelow.

2C. Silver Sulfadiazine (AgSZ)- in AQ

Crosslinked elastomer hydrogel AQ tubing was prehydrated for one day at body temperature. Several stands were placed in a blackened polyethylene tube, as described in Example 2A above, and the strands were immersed in cold 1.5 wt% silver nitrate (Aldrich Chemical Co.) solution and allowed to soak in the dark at 4°C. After about 2½ hours, fresh silver nitrate solution was added. After six additional hours, the solution was decanted and a cold (when the term cold is used herein it refers to a temperature of about 4°C.) 2.4 wt% solution of NaSZ was added. One half hour later, the NaSZ solution was exchanged for fresh NaSZ solution and left for 15 hours. The tubing was rinsed with water, immersed for 5 minutes in pH 7 buffer, rinsed with water, blotted dry and stored in a desiccator in the dark. Contrary to the teaching of U.S. Patent 4,612,337, the conditions of reduced temperature and sufficient time to penetrate the tubing matrix are significant for the quantity of

medicament incorporated and appearance of article (4,612,337, Ex 2). The resulting white tubing was calculated to contain about 1 wt% Ag (as AgSZ) and about 2.4 wt% NaSZ.

2D. AgSZ in AQ. Crosslinked AQ tubing samples were coiled in an amber bottle and cold 1.6 wt% silver nitrate solution was added. After four hours the nitrate solution was replaced with fresh solution. Twelve hours later, the tubing was rinsed with cold water and cold 2.5% NaSZ added and then replaced after five hours. Four hours after that the tubing was rinsed with water, soaked in pH 7 buffer for four hours at room ambient temperature, blotted and cut into approximate one inch pieces which where kept in a desiccator in the dark. The AgSZ impregnated tubing was calculated to contain about 1 wt% Ag (as AgSZ) and 2.5 wt% NaSZ and was initially a light tan color.

2E. AgSZ made on Polyurethane. This example was made following the teachings of U.S. 4,581,028, Example 3. Two strands of non-swelling hydrophobic polyurethane tubing (PU) (made from Thermedics, 100A resin) were immersed in a 30 micromolar solution of NaSZ for one hour. The tubing was blotted dry and immersed in an equimolar silver nitrate solution for 10 minutes, rinsed in water, blotted dry, air dried for an hour in the dark and stored in a desiccator at 4°C. As the polyurethane was of the non-swelling variety it was impossible to calculate the amount of medicament adsorbed on the surface of the tubing.

2F. AgSZ on PU. This example is similar to example 2E above except the concentrations of the reagents were increased by over three thousand fold to use a silver nitrate solution of 1% Ag which is a similar level to other silver compounds in examples 2A-D and 2G. Thus 93 millimolar solutions of NaSZ and $AgNO_3$ were used. The tubing was allowed to dry before the final rinse step. As the polyurethane was of the non-swelling variety it was impossible to calculate the amount of medicament adsorbed on the surface of the tubing.

2G. AgSZ on Silicone (Si) A four foot piece of hydrophobic non-swellable polydimethylsiloxane tubing (Dow Corning Silastic Rx50 medical grade) was coiled into a two ounce amber bottle and filled with cold 1.6 wt% $AgNO_3$ and kept in the dark at 4°C. for about five hours. Then the solution was discarded and fresh silver nitrate solution added, the tubing was kept immersed at 4°C. for another 19 hours. The tubing was washed gently with water and a cold 2½ wt% solution of NaSZ added. After four hours the NaSZ was replaced with fresh solution. Six hours later the NaSZ solution was decanted and the tubing was rinsed inside and out with pH 7 buffer and soaked in buffer for five hours. Then the tubing was rinsed inside and out with water, gently blown dry inside with air, blotted dry and stored cold in a desiccator in the dark. Later some of the tubing was cut into 2 to 2½ cm segments and stored as above. As the material was of the non-swelling variety it was impossible to

calculate the amount of medicament adsorbed on the surface of the tubing. Thus, although the concentrations of reagents used in this example are the same as that of most of the tubings described in Example 2 the actual amount of AgSZ and NaSZ incorporated on (or just inside) the tubing surface is unknown.

2H. AgSZ in Hydrophilic Polyurethane. A water swellable hydrophilic polyurethane (HPU) which swells nearly 6 times in volume upon hydration was prepared by a one shot process similar to that described in Example IX of U.S. Patent 4,359,558. This HPU contains 66% polyethylene glycol (MW 7500), 1.8% diethylene glycol, 20% diethylene glycol diacrylate and 12% aliphatic diisocyanate and a small amount of stabilizer. The resulting resin was extruded into tubing and exposed to 2½ megarad of electron beam radiation.

Two about 2 foot long strands of this tubing were coiled into a two ounce amber bottle and treated identically as the tubing in Example 2G above. Short segments were also stored in an open amber vial at 4°C. in a desiccator in the dark. This highly swollen tubing was calculated to contain about 4 wt% Ag (calculated as $AgNO_3$).

2I. Silver Nitrate Control. Strands of crosslinked AQ tubing were coiled into a two ounce amber vial and immersed in a cold solution of 1.10g silver nitrate and 68.89g water and held for ten hours at 4°C. The silver nitrate solution was decanted; the tubing was rinsed then immersed in water for

twenty minutes, blotted dry, and stored in an open vial in a desiccator at 4°C. in the dark. This tubing was calculated to contain approximately 1 wt% Ag as $AgNO_3$.

Example 3 In Situ Formation of Silver Halides

3A. Silver Chloride. Procedures similar to those described in Example 2C were utilized. Dry tubing was soaked in 1.6 wt% cold silver nitrate solution for just over four hours, rinsed with water and a 3% solution of sodium chloride (J.T. Baker, Inc.; 99.6%) added and left overnight. The tubing was rinsed with water and soaked in PBS for five hours at room temperature, rinsed again with water, air dried in the dark and stored in a desiccator in the dark. This tubing was calculated to contain approximately 1 wt% Ag as AgCl.

3B. Silver Bromide. The same procedures as in Example 3A were followed, except 5.3% sodium bromide (J.T. Baker, Inc.; 99.3%) solution was added (instead of sodium chloride) and the finished product was allowed to equilibrate in PBS for 8 hours prior to drying. About 1 wt% Ag, as silver bromide, was calculated to be present in the tubing.

3C. Silver Iodide in AO. Identical procedures to those described in Example 2D were followed except that a 1.2 wt% lithium iodide (Sigma Chemical Co.) was added instead of the NaSZ. The tubing was white in color and was

calculated to contain 1 wt% Ag as AgI disbursed throughout the elastomer hydrogel matrix.

3D. Melt Blended Silver Chloride. Silver chloride, (Aldrich Chemical Co,) 1.2 wt%, was mixed with AQ pellets prior to extrusion. Although silver chloride has a melting point much higher than the temperatures used in extrusion, the resulting material had an orange brown color and could not be further processed. Its properties (color, texture) were clearly such as to be commercially unacceptable.

Example 4 Solubility Change of Medicament by pH Change

4A. Doxycycline Free Base. Several strands of crosslinked AQ tubing were turned into about 2½ inch coils and placed in a vial with the tubing ends protruding. The vial was filled with cold 2.3 wt% solution of doxycycline hydrochloride (DHC) (Sigma Chemical, 847 units doxycycline base/mg, pH 2.3) The tubing absorbed solution containing a total of about 0.83 mmoles of DHC for three and one half hours. DHC has a solubility of about 300 mg/ml.

Doxycycline hydrochloride is amphoteric; it is least soluble at pH's around 5 to 6 and more soluble at higher or lower pH's. Formation of doxycycline free base (DFB) inside the tubing matrix was accomplished by adding sufficient sodium hydroxide to a pH 5.7 hydroxide-phosphate buffer to react with

the measured amount of DHC. This buffer/base solution was composed of 2.44g potassium dihydrogen phosphate, 30.70g water, and 1.45g sodium hydroxide.

The DHC solution was decanted and the tubing strands were rinsed with dilute (9:1) buffer solution. The tubing was immersed in the above buffer/base solution for about five hours with intermittent agitation. The pH of the solution was about 5.7. Next the tubing was rinsed and immersed in water. The pH measured about 5.4. After three hours, the tubing was blotted dry and cut into roughly 3 cm long segments and stored in a desiccator at 4°C. This procedure resulted in about two percent free doxycycline base being deposited throughout the elastomer hydrogel matrix. The tubing was very light yellow. At the pH values used DFB was expected to be much less soluble than DHC.

4B. Doxycycline Hydrochloride. Crosslinked AQ tubing strands were looped into a glass vial as described above and immersed in a 10% DHC (8.5 % active) solution. After three hours the solution was replaced with fresh DHC solution. After three and a half hours, the tubing was rinsed several times with water, blotted dry on lint free towels cut into ~3 cm pieces and dried in a desiccator. The yellowish tubing was stored at 4°C. in a desiccator and contained approximately 8.5 wt% DHC.

Example 5 Solubility Change Via In Situ Salinification

This example illustrates the process of salinification by the reaction of polymyxin B sulfate (Pmyx) with organic acids forming a polymyxin salt complex. Various n-alkyl carboxylic acids were separately reacted with polymyxin B sulfate by adding Pmyx solution to a slight excess (over the 5 times molar ratio required) of the dissolved sodium acid salt. In this way the solubilities of the resulting complexes can be tailored for specific applications. Acid derivatives investigated in glassware included acetic, caproic, caprylic, capric and myristic. Sodium caprylate was chosen since it was of low solubility but was not completely insoluble.

5A. Polymyxin Caprylic Acid Complex. Three approximately 3½ foot crosslinked AQ tubing segments were wound into loops and each was placed in a separate 16 ml vial with the ends outside. Caprylic acid, sodium salt (Sigma Chemical Company) solution (1.4g/100g) was added to the vials, immersing the tubing. After 2 hours the tubing was rinsed and the vials were refilled with more solution and allowed to soak for over 2½ hours. The tubing was rinsed twice with water and then immersed in Pmyx solution (Sigma Chemical Company, 8090 units/mg) (2.0g/100g solution). After 3 hours, fresh Pmyx solution was added. After nearly 3 more hours the tubing was washed with water, blotted dry, cut into 1 to 1½ inch pieces and stored in a desiccator. This tubing was calculated to contain about 3.2 wt% of the polymyxin caprylate complex and about 2 wt% of polymyxin B sulfate.

5B. Polymyxin B Sulfate Control. This tubing was prepared as described in Example 5A, except the caprylic acid solution steps were omitted. This tubing was calculated to contain about 2 wt% of soaked in polymyxin B sulfate.

Example 6 In Situ Water Soluble to "Insoluble" Derivative

6A. Chlorhexidine Digluconate Impregnated AQ Tubing. A five percent aqueous solution of chlorhexidine digluconate (CDG) was prepared by diluting a 20% solution (Sigma Chemical Co.). Several 26 inch strands of crosslinked AQ tubing were coiled into a 2 ounce amber bottle and immersed in the 5% CDG solution with the ends protruding. After 4½ hours the solution was decanted and fresh 5% CDG solution was added. After 3 additional hours the tubing strands were removed from solution, blotted dry on lint free towels and dried in a desiccator. The tubing was calculated to contain about 5% CDG.

6B. Chlorhexidine Diacetate Impregnated AQ Tubing. Saturated solutions of chlorhexidine diacetate dihydrate (CAc) (Aldrich Chemical Co.) were prepared by stirring 4.02g CAc with ~260 ml of water. This cloudy solution was poured into a 4 oz vial containing six coiled lengths of crosslinked AQ tubing and stirred for 6 hours. The solution was discarded and fresh saturated CAc solution was added and stirred overnight. The tubing was rinsed by immersion in water for several

minutes, blotted dry and further dried in a desiccator. This material was calculated to contain about 1.5 wt% CAc.

6C. CAc on Polyurethane Tubing. The same procedure was used as in example 6B except the tubing was soft non-swellable and non-hydrophilic polyurethane (resin from Thermedics, 100A grade). Swelling did not occur and it was not possible to calculate the amount of CAc on the surface of the tubing.

6D. Chlorhexidine Dichloride (CCl) made in situ from CDG impregnated AO. AQ tubing strands from Example 6A were taken before the drying step, coiled into a 2 ounce bottle and immersed in 0.1N HCl for almost 3 hours with the ends protruding. The HCl solution was then decanted and fresh HCl solution replaced it for an additional 2¼ hours. The tubing was removed from the HCl solution and was then soaked in pH 7 phosphate buffer overnight; rinsed with and then soaked in PBS for 30 minutes; soaked in water for 2 hours; blotted dry; and further dried under vacuum at 44°C. for 7 hours. The tubing was calculated to contain about 3.2 wt.% CCl.

6E. CCl made in situ from CAc impregnated AO. AQ tubing strands from example 6B were looped into a vial and immersed in 0.1N HCl for 30 minutes with the ends protruding, rinsed briefly several times with water, blotted and sealed at 100% relative humidity (RH) for two hours. A distinct acetic acid odor was present indicating replacement of acetate ion

by chloride ion. The tubing was reimmersed in fresh hydrochloric acid for four hours, rinsed with water and soaked in PBS for 1 hour. It was then removed from solution and kept at 100% RH for just over eight hours after which it was placed in pH 7 buffer.

After two hours the buffer was decanted, the tubing rinsed with water then immersed in PBS for 6 hours. Finally the tubing was rinsed several times with water, blotted dry and stored in a desiccator. This tubing was estimated to contain about 1 to 1.5 wt% CCl.

6F. CCl made on Polyurethane (PU). Short segments of non-swelling non-hydrophilic PU tubing with CAc from example 6C were immersed in 0.1 N HCl for four hours, rinsed with water, then pH 7 buffer and immersed in buffer for three hours with the ends protruding. Some pieces were placed in a vial and continuously extracted (see below) and the rest were blotted dry and stored in a desiccator. Swelling did not occur during the example 6C step and it was not possible to calculate the amount of CCl on the surface of the tubing. This example is representative of the procedure of Japanese patent publication JP 6036064.

6G. CCl made on Si Tubing. Four feet of the silicone tubing described in Example 2G, coiled in an amber vial was immersed in saturated (~1.5 wt%) CAc solution at room temperature for five hours. The solution was replaced with fresh saturated CAc solution and left for 19 hours. The tubing was rinsed

gently inside and out with water, blown dry inside, blotted dry and placed in a desiccator to partially dry for three hours. The tubing was gently re-coiled into an amber vial and immersed in 0.1N HCl for one half hour, after which the tubing was washed as above with water and kept damp at 100% RH for two hours. The tubing was recoiled and reimmersed in fresh 0.1 N HCl for five additional hours. Again the acid was decanted and tubing rinsed inside and out with pH 7 buffer followed by forty five minute immersion in buffer. The tubing was again washed with water and kept at 100% RH overnight. The silicone tubing was rinsed inside and soaked with neutral buffer for two hours, flushed again with water, soaked one hour in PBS, rinsed in water, blown and blotted dry and stored in a desiccator. This is similar to the procedure used in Example 6E above. Swelling did not occur during the CAc contacting step and it was not possible to calculate the amount of CCl on the surface of the tubing. This example is meant to be representative of the procedure of Japanese patent publication JP 6036064.

6H. <u>CCl in situ in HPU.</u> The hydrophilic polyurethane tubing described in Example 2H was used in this example. The CCl was made in situ by reacting HCl with CAc using the identical procedures described in Example 6G above. The tubing is calculated as containing approximately 7 wt% of incorporated CCl.

Example 7 Non Aqueous Impregnation of Medicament.

This example demonstrates the use of non-aqueous impregnation of a hydrophilic matrix by a medicament which is soluble in a non-aqueous solvent system and is substantially insoluble in water. Oxytetracycline (OXY) has a solubility in methanol of 18.5 mg/ml and in water of 0.6 mg/ml (Weiss et al, Solubility of Antibiotics, Antibiotics and Chemotherapy, Vol VII, No. 7, July 1957). Water swellable hydrophilic articles with long lasting antibacterial activity were constructed as set forth in following.

7A. Oxytetracycline impregnated tubing. A saturated methanol solution of OXY (Sigma Chemical Co.) was made by stirring 2.87g OXY in 106.1g methanol overnight and filtering the milky solution to form a clear amber OXY solution. Crosslinked AQ samples were coiled, placed in a small vial and immersed in the saturated OXY/methanol solution with the ends protruding. The vials were sealed loosely with parafilm and the tubing was soaked for about seven hours. The tubing was rinsed briefly with pure methanol, dried in air and stored in a desiccator before being cut into short pieces for extraction testing. The tubing was calculated to contain about 1.8 wt% of the antibiotic.

7B. Methanol Control. Segments of tubing were treated as in Example 7A above except only pure methanol was used. The dry tubing showed only very slight initial antibacterial activity (<0.1 mm zones, see below) with no antibacterial activity at all after 1 day

extraction. This example was carried out to show that the antibacterial effectiveness of the tubing of Example 7A was not due to the presence of residual methanol used in the process.

Examples 8-23
Microbiological Activity Testing.

Example 8 Activity of AO with soaked in gentamicin (Ex 1B).

Short 2 cm tubing segments from example 1B and untreated control tubing were separately soaked in water for the time periods shown in Table I. The individual tubing pieces were rinsed (except dry samples) inside and out with water; blotted dry outside, blown dry inside, placed in pairs or in triplets on an agar plate and immersed in 20 ml of warm 45-60°C nutrient agar solution. The agar had been seeded with about 1 x 10^8 colony forming units (CFU) of bacillus subtilus. The plates were incubated overnight (19-24hr) at 30°C.

A clear generally rectangular zone surrounding the tubing in the otherwise cloudy plate, indicates the effectiveness of the antibiotic, which diffused from the tubing, in killing or inhibiting the growth of the organism. The zone sizes of two or three pieces, measured near both ends and in the middle, are averaged and presented in Table I. The outer diameter (OD) of the tubing was about 0.9 mm dry and 1.3 mm hydrated. Zone sizes are given to the nearest 0.5 mm and the diameter of the tubing has been subtracted.

Table I

Activity of tubing from Example 1B

		Zone Size, mm		
Extraction Time, hours	0(dry)	5	17	22
Example 1B	12.5	9	5	5
Control	0	0	0	0

A standard gentamicin solution (10 µg/ml) placed in an approximate one mm diameter trough in the agar, gave a net zone of 6.5 mm. This example shows that tubing containing 5% of water soluble antibiotic maintains activity for about one day. Example 10, discussed below, extends this data and shows that this activity diminished to zero in about one week.

Examples 9-14 Activity of Impregnated AO vs. B. Subtillus.

Table II summarizes the results from PBS extraction for the time indicated for various impregnated tubing examples described above. Pairs of tubing specimens in 12 ml vials were extracted in PBS for varying time internals indicated. The PBS solutions were decanted and replaced with fresh solution every day or two on average. The antibacterial activity was evaluated as described in Example 8 except 10 ml of nutrient agar solution was used and after two days only a single piece of tubing was evaluated.

Table II

Inhibition Zone Surrounding AO Tubing

Inhibition Zone[a], mm

Extraction Time, hours		0[d]	1	3	5	18	44	61	113	168	230	262	291
	Example												
9	2B (control)	-	0	0	0	0	0	0	0	0	0	0	-
10	1A (Genta)	-	9.5	9.5	9.5	7	3.5	3	2	1.5	0	-	-
11	2A (NaSZ)	t	0	0	0	0	0	0	0	0	-	0	-
12	2C (AgSZ)	8.5	6.5	6.5	6.5	7	6.5	6.5	7	6.5	-	7.5	9[b]
13	3A (AgCl)	-	6.5	6.5	6.5	7	6	-	-	-	-	-	-
14	3B (AgBr)	-	5	-	6	6.5	5	-	-	-	-	-	-

a. excludes tubing diameter, b. different agar stock

t = trace d = dry

Example 9 shows that neither the virgin untreated tubing, the PBS solution, not the procedures used had any inhibiting effect against the Bacillus.

Example 10, with tubing containing about 1.5 wt% gentamicin sulfate (565μg/mg) incorporated into the tubing during melt processing, demonstrates that this material was completely extracted out of the tubing in 7-10 days. This is typical of water soluble substances, whether incorporated during processing as in this example or incorporated by soaking in as in Example 1 (results shown in Example 8).

Example 11 shows that 2.2 wt% sodium sulfadiazine in the tubing has virtually no activity against the organism even when dry and before any leaching has taken place. This proves that the activity of AgSZ impregnated tubing is not due to residual NaSZ left by the in situ AgSZ forming process.

Example 12 shows AgSZ containing swellable hydrophilic tubing maintains effective activity for over 291 hours. The elastomer hydrogel AQ tubing acts as a reservoir for the relatively insoluble silver sulfadiazine resulting in a fairly constant slow release. Various examples below prove the "insoluble" medicaments can be effective for much longer periods of time when incorporated by this in situ process. See examples 15, 19A, 19C and 19D below for results of much longer extraction times with silver compounds.

Examples 13 and 14 show that in situ formed silver chloride and bromide have effective antibacterial activity for more than two days. See example 16 for results with AgCl after a longer extraction time.

Examples 15 and 16
Long Term Activity of
AgSZ and AgCl AO Tubing

Table III gives zone sizes for tubing from Examples 2C and 3A. The one inch tubing samples were extracted in small (8ml) vials by PBS, which was changed every 48 or 72 hours. This is an extension to longer time periods of Examples 12 and 13 above. These examples prove that by incorporating antibacterial silver salts in situ inside the elastomer hydrogel matrix, the tubing shows significant microbiological activity for over 100 days.

Table III

Long term Activity of AO containing Silver Salts

Inhibition Zone, mm

Extraction Time, days		14	17	20	24	26	28	31	33	35	38	45	73	102
Example														
15	2C,AgSZ	10	8	10	8.5	8.5	7.5	7.5	11	8	8.5	8	7	8.5
16	3A,AgCl	8	8	7	9	9	8	8	9	8	8	8	7	8.5

Example 17 Activity of a Soluble Silver Salt in AO Tubing

Tubing described in Example 2I was tested to demonstrate that the prolonged activity of the material containing the silver salts described in examples 15 and 16 was not an artifact of specimen preparation during the silver nitrate impregnation step. No residual silver nitrate is expected as it should be completely reacted (or diffused out) by the procedures used. The tubing samples prepared in Example 2I were cut into one inch pieces, placed into 8ml amber vials and continuously flushed by pumping distilled water continuously at approximately 0.4 ml/min through the vial. At periodic intervals tubing specimens were removed, stored in water in sealed vials for 1 day then analyzed for microbiological activity as described for Example 9. Extraction times/zone sizes are as follows: dry/6.6 mm.; 1 day/6.6 mm.; 3 (and more) days/0 mm. This experiment demonstrates that the activity of any insoluble silver salt used in these examples cannot be due to residual silver nitrate or any unexpected silver-tubing complex.

Example 18 Medicament Loaded AO vs. Staph Epi Solutions.

18A. 4 Day Incubation. Medicament loaded tubing segments (a single 1-1½ inch long piece per tube), extracted for the indicated times, were immersed in 2 ml of staphylococcus epidermidis (~500 CFU/ml) in a small test tube and incubated for various time periods as shown in Table IV. If there is insufficient antibiotic eluting from the already extracted tubing to kill all the organisms, then they will multiply causing the solution to become turbid. This turbidity or cloudiness is graded on a scale of 0 (clear) to 4+ (cloudy). Table IV shows the effectiveness of the indicated tubing specimens in retarding or eliminating the growth of Staph Epi. Duplicate tubing samples of Examples 9-12 (also shown in Table II) were used.

Table IV

Turbidity of Extracted Drug
Containing AQ Tubing vs. Staph Epi

Scale: 0 = clear; 4+ = cloudy

Extraction Time, hours	dry	4	7	10	22	48	66	118	173	235	267
Example											
20 hour incubation											
2B (control)	-	4+	-	-	-	-	-	-	-	4+	-
1A (Genta)	0	0	0	0	2+	2+	4+	4+	4+	-	4+
2A (NaSZ)	0	0	4+	4+	4+	4+	4+	4+	-	4+	-
2C (AgSZ)	0	0	0	0	0	0	0	0	0	-	0
42 hour incubation											
1A (Genta)	0	4+	4+	4+	4+	4+	4+	4+	4+	-	4+
2A (NaSZ)	0	2+	4+	4+	4+	4+	4+	4+	-	4+	-
2C (AgSZ)	0	0	0	0	0	0	0	0	0	-	0
4 days incubation											
1A (Genta)	0	4+	4+	4+	4+	4+	4+	4+	4+	-	4+
2A (NaSZ)	4+	4+	4+	4+	4+	4+	4+	4+	-	4+	-
2C (AgSZ)	0	0	0	0	0	0	0	0	0	0	0[a]

a. Has some non-staph bacterial growth from contaminated PBS

NaSZ is not present in effective antibacterial concentrations. For example, tubing from Example 2A (NaSZ only) was soaked for 4 hours in PBS. This tubing was immersed in the Staph Epi solution. No growth of the bacteria was observed after 20 hours incubation, moderate growth after 42 hours and excessive growth within four days. This indicates that the NaSZ solution did not inhibit organism growth and the activity of Example 2C is not due to the NaSZ also present. The dry gentamicin sulfate loaded tubing (Example 1A) elutes sufficient antibiotic (burst effect) to kill all Staph Epi organisms present and thus none exist to multiply during incubation periods. In contrast the NaSZ dry tubing elutes less than a lethal dose and turbidity appears within four days. The AgSZ impregnated tubing (Example 2C) has excellent antibiotic activity; even samples pre-extracted for 267 hours maintain sufficient activity to kill the Staph Epi present and the solution remains clear.

18B. 21 Day Incubation. This test is similar to that described in Example 18A above. Pieces (1 to 2 inches long) of tubing from Example 2C (AgSZ) which had been extracted for 267 hours were placed in separate solutions containing 5×10^3, 5×10^4, 5×10^5, and 5×10^6 CFU/2ml, respectively, and incubated for up to 21 days. Break through, or the time for turbidity (score $\geq$ 4+) to develop, occurred after three days at the highest CFU level, and 15 days at 5×10^5 CFU/ml. No growth of Staph Epi was observed at the other

two levels and the solutions remained clear. The silver sulfadiazine impregnated tubing, extracted for over 11 days, effectively inhibited growth of Staph Epi at clinically relevant concentrations.

Examples 19 Activity of Insoluble Silver Derivatives-Continuous Extraction of Silver Derivative Loaded Tubing Samples.

Tubing samples in this example (except Example 19C) contained in 8 ml amber vials were continuously washed with BNS (buffered normal saline) at about 0.4 ml/min, removed at stated time intervals, then analyzed as described in Examples 17 and 9. There is some variability in zone sizes measured at different times, but the trends, shown by the lines of Figure 1, are clear. A regular shift was noted in the data at the end of one time period. This is believed to be due to compositional fluctuations of the concentration of the bacteria containing nutrient agar solutions being different. To measure this variability, later experiments (Examples 17, 19 (except 19C), 20, 22 and 23) utilized a gentamicin containing disc as a standard. This control disc is a Kirby Bower pellet containing 10 micrograms of gentamicin. The discs are about 6 millimeters in diameter and net zone sizes ranged from about 5½ to 6 mm from the edge of the disc to the edge of the bacteria clear circle.

19A. AgSZ in AQ. Tubing from Example 2D was used for this Example. Figure 1 shows that tubing containing silver sulfadiazine formed in situ in the elastomer hydrogel AQ tubing retains activity for about 160-180 days of constant saline flush (~2 ml/min for the first 50 days in buffered tap water then ~0.4 ml/min in BNS). This continuous flow situation is more

relevant to actual applications as in vascular or urinary catheters, than is the static soaking of most examples in the prior art. (Compare to example 19C below)

19B. AgI in AO. This example was run in parallel with Example 19A except tubing from Example 3C was used. This silver iodide impregnated tubing maintains antibiotic activity for about three months. These results are also presented in Figure 1.

19C. AgSZ in AO-Periodic Extraction. This example duplicates Example 19A except the extracting solution was changed on a daily basis for the first fifty days and five times per week thereafter. Figure 1 shows that this periodic solution exchange does not deplete the drug as quickly as the continuous flush. It maintains antibiotic activity for more than 200 days, emphasizing again that the static extraction of most of the prior art overestimates the effectiveness of antibiotic activity compared to more realistic continuous extraction.

19D. AgSZ in Hydrophilic Polyurethane. Tubing from Example 2H was continuously extracted in BNS at ~0.4 ml/min and was then tested for activity against bacillus subtilis as previously described. The results are given in Figure 1. This example shows that silver sulfadiazine prepared in situ in this water swollen hydrophilic polyurethane maintains antibiotic activity for seven to eight weeks even under continuous flow conditions.

19E. AgSZ on Hydrophobic Polyurethane. Dry (non-extracted) tubing from Example 2E was tested for activity against bacillus subtilis as described in Example 9. This dry tubing possessed no antibiotic activity even when tested dry. This tubing was made following the teaching of U.S. Patent 4,581,028 using hydrophobic (contains about 1 wt% moisture) aliphatic polyurethane tubing. This demonstrates the vast improvement of the present invention.

19F. AgSZ on Hydrophobic Polyurethane This example is the same as 19E above, except the concentration of reagents was increased to the levels of other silver containing examples discussed in this application per Example 2F. This concentration which provides 1 wt% silver in AQ tubing is over 3,100 times higher than the example disclosed in the referenced patent. In this case the dry tubing yielded only a small 1.2 mm zone. This hydrophobic polyurethane tubing, prepared by the teachings of the prior art but with increased antibiotic levels, lost all antibiotic activity after merely static soaking for less than 24 hours.

19G. AgSZ on Silicone Tubing Tubing from Example 2G was tested for antibacterial activity. The dry non-extracted tubing yielded a clear zone of about 5mm. Within two days simply

static soaking in a small vial, the tubing pieces lost all of their activity.

Examples 19 E, F, G are examples of prior art on polyurethane or silicone tubing and have antimicrobial activity for extremely short times, if at all. Examples 19 A-D of the present invention have significant antimicrobial activity for several weeks to months and longer, even when continuously flushed with saline solution.

Example 20 Antibiotic Activity via in situ pH Precipitation.

Following the same procedures as described for Example 19, tubing segments from Example 4 containing doxycycline derivatives were tested for antibiotic activity after continuous extraction for various time intervals. The results are shown graphically in Figures 3 and 4. In this case the in situ synthesis technique was used to increase the diffusability of the base antibiotic. The result was surprising since DFB, at the pH in question, was expected to be significantly less soluble than DHC. The DHC was used at an 8% by weight concentration while the DFB was used at a 2% by weight concentration.

Example 21 Antibiotic Activity After in situ Salinification.

Tubing segments from Examples 5A and 5B were soaked in PBS, with periodic replenishment with fresh PBS solution. Segments which had been extracted for various time periods were tested against bacillus subtilus as described in Example 19C above. The tubing with the less soluble polymyxin-caprylic acid

complex maintained measurable antibiotic activity for approximately twice as long as the more soluble polymyxin B sulfate impregnated tubing.

Example 22 Antibiotic Activity of Chlorhexidine Derivatives.

Segments of various tubing samples described in Example 6 were placed in a small vial, continuously extracted for various time periods, then analyzed for antibiotic activity. The extraction and analytical procedures were the same as those described in Examples 17 and 9 respectively. As for the cases of gentamicin (Example 10) and silver nitrate (Example 17), the highly water soluble chlorhexidine digluconate impregnated AQ tubing showed limited activity for a short time only. The results are shown in Table V below for the tubing from Example 6A.

Table V

Activity of AO containing 5% CDG

Extraction time, days	0(dry)	1	3	7	13	21
Zone size, mm, net	10.1	13.8	8.6	7.6	2.5	0

The CCl containing AQ tubing, made from the CDG tubing, showed zone sizes in the 5-9 mm range throughout the same time period. For this time period its behavior tracked the longer time performance of the CCl AQ tubing of Example 6E discussed immediately below and shown in Figure 2.

The results are shown in Figure 2 for tubing from examples 6B, 6E, 6F and 6H. The water swelling polymers (from Examples 6B, 6E and 6H) showed good activity: about 1 month for HPU of Example 6H and least several months for AQ samples of Example 6E. Chlorhexidine chloride precipitated onto the non-swelling silicone tubing of Example 6G had no activity at any time and does not appear in Figure 2. The hydrophobic polyurethane of Example 6F showed some activity but all activity disappeared after about one day of extraction. It was very surprising to note that while CAc has higher solubility (1.9g/100ml) than does CCl (0.06g/100ml) it exhibited higher activity for much longer periods of time (more than 200 days).

Example 23 Comparative Example with Solvent Imbibed Antibiotic.

This example shows how the technique illustrated in Example 7A allows preparation of AQ tubing possessing long lasting antibiotic protection. This tubing was extracted and tested using the same procedures as described in Example 19C. This tubing maintains antibiotic activity against bacillus subtilis equivalent to 10μg gentamicin for over 200 days (see Figure 5).

Industrial Applicability

The present invention provides a method of incorporating chemicals, particularly medicaments, in hydrophobic matrixes in controllably soluble form whereby the medicaments can be delivered over a selectively long period of time. Articles having these properties can be used as slow time releases for medicaments and are particularly useful for forming cannulae, particularly water swellable cannulae.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modification, and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice in the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as fall within the scope of the invention and the limits of the appended claims.

Claims

That which is claimed is:

1. A method of incorporating a chemical in a swellable hydrophilic matrix, comprising:

contacting the matrix with a solution having the chemical or a precursor of the chemical dissolved therein, the solution including a solvent which is selected to swell the matrix by at least 10% in volume and sufficient of the precursor or of the chemical to provide a desired level of the precursor or of the chemical dispersed throughout the matrix; and thereafter

depositing the chemical in the matrix in a form in which it exhibits a selectable aqueous solution solubility.

2. A method as set forth in claim 1, wherein the hydrophilic matrix swells at least 20% in volume when contacted by the solution.

3. A method as set forth in claim 1, wherein the hydrophilic matrix swells at least 50% in volume when contacted by the solution.

4. A method as set forth in claim 1, wherein the solvent comprises a non-aqueous liquid and the depositing comprises removing the non-aqueous liquid.

5. A method as set forth in claim 4, wherein the matrix is in the form of a cannula.

6. A method as set forth in claim 1, wherein the solvent is water and the solution contains a precursor of the chemical and wherein the depositing comprises:

1) converting the precursor, in situ in the matrix, to the chemical.

7. A method as set forth in claim 6, further including the step of removing the water.

8. A method as set forth in claim 7, wherein the matrix is in the form of a cannula.

9. A method of incorporating a medicament in a preformed medical device comprising a swellable hydrophilic matrix, comprising:

contacting the matrix with a solution having the medicament or a precursor of the medicament dissolved therein, the solution including a solvent which is selected to swell the matrix by at least 10% in volume and sufficient of the precursor or of the medicament to provide a desired level of the precursor or of the medicament dispersed throughout the matrix; and thereafter

depositing the medicament into the matrix in a form in which it exhibits a selectable aqueous solution solubility in such a manner that it has therapeutic effectiveness only in a narrow zone around the matrix but the effectiveness lasts for an extended period of time.

10. A method as set forth in claim 9, wherein the hydrophilic matrix swells at least 20% in volume when contacted by the solution.

11. A method as set forth in claim 9, wherein the hydrophilic matrix swells at least 50% in volume when contacted by the solution.

12. A method as set forth in claim 9, wherein the solvent comprises a non-aqueous liquid and the depositing comprises removing the non-aqueous liquid.

13. A method as set forth in claim 9, wherein the device is in the form of a cannula.

14. A method as set forth in claim 9, wherein the solvent is water and the solution contains a precursor of the medicament and wherein the depositing comprises:

1) converting the precursor, in situ in the matrix, to the medicament.

15. A method as set forth in claim 14, further including the step of removing the water.

16. A method as set forth in claim 15, wherein the device is in the form of a cannula.

17. A method as set forth in claim 15, wherein the region of effectiveness is no more than about 50mm and the extended period of time is at least 5 days.

18. A method as set forth in claim 17, wherein the extended period of time is at least 10 days.

19. A method as set forth in claim 17, wherein the extended period of time is at least 30 days.

20. A method as set forth in claim 17, wherein the region of effectiveness is no more than about 25mm.

21. A method as set forth in claim 20, wherein the extended period of time is at least 10 days.

22. A method as set forth in claim 20, wherein the extended period of time is at least 30 days.

23. A method of incorporating a medicament which is substantially insoluble in water in a preformed medical device comprising a swellable hydrophilic matrix, comprising:

contacting the matrix with a solution having the medicament dissolved therein, the solution including a solvent which includes a non-aqueous component and is selected to swell the matrix by at least 10% in volume, the solution further including sufficient of the medicament to provide a desired level of the medicament dispersed throughout the matrix; and thereafter

removing the non-aqueous component and thereby depositing the medicament into the matrix.

24. A method as set forth in claim 23, wherein the non-aqueous component is methanol, ethanol, formamide, acetone, tetrahydrofuran, dimethyl formamide, dimethylacetamide, methylene chloride, ethyl acetate 1-methyl-2-pyrolidinone, dimethylsulfoxide, sulfolane, methyl ethyl ketone, γ-butyrolactone, diethylcarbonate, ethylene carbonate or the like and mixtures thereof with each other and/or with water.

25. A method as set forth in claim 23, wherein the device is in the form of a cannula.

26. A method of providing a preformed medical device which comprises a swellable hydrophilic matrix with long lasting antibiotic effectiveness, comprising:

absorbing chlorhexidine acetate into the matrix.

27. A method as set forth in claim 26, wherein the device is in the form of a cannula.

28. A method as set forth in claim 26, further including:

converting the chlorhexidine acetate to a chlorhexidine halide.

29. A method as set forth in claim 28, wherein the device is in the form of a cannula.

30. A medical device comprising:

a swellable hydrophilic matrix which swells at least 10% in volume on immersion in water and which has uniformly dispersed throughout a substantially water insoluble medicament and being characterized in that the medicament is dispersed in the matrix in such a manner that it exhibits therapeutic effectiveness for at least 5 days.

31. A medical device as set forth in claim 30, wherein the device exhibits therapeutic effectiveness for at least 10 days.

32. A medical device as set forth in claim 30, wherein the device exhibits therapeutic effectiveness for at least 30 days.

33. A medical device as set forth in claim 30, wherein the device comprises a cannula.

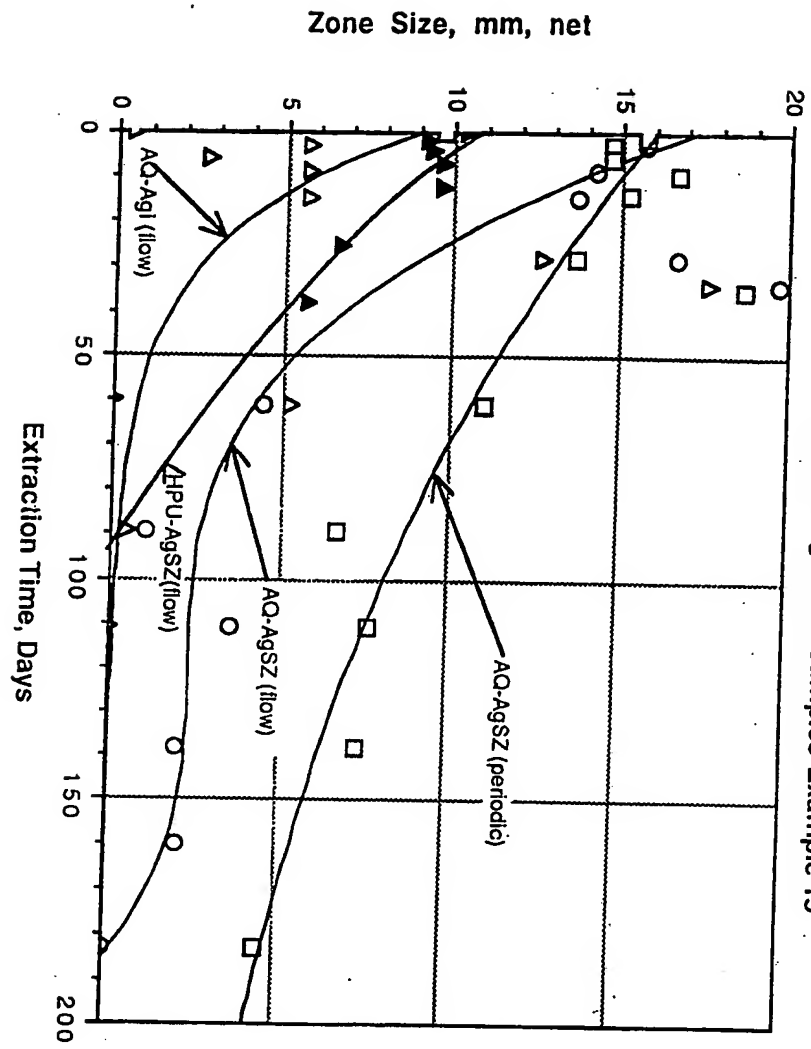

FIGURE 1

AQ with Long Acting Silver Samples-Example 19

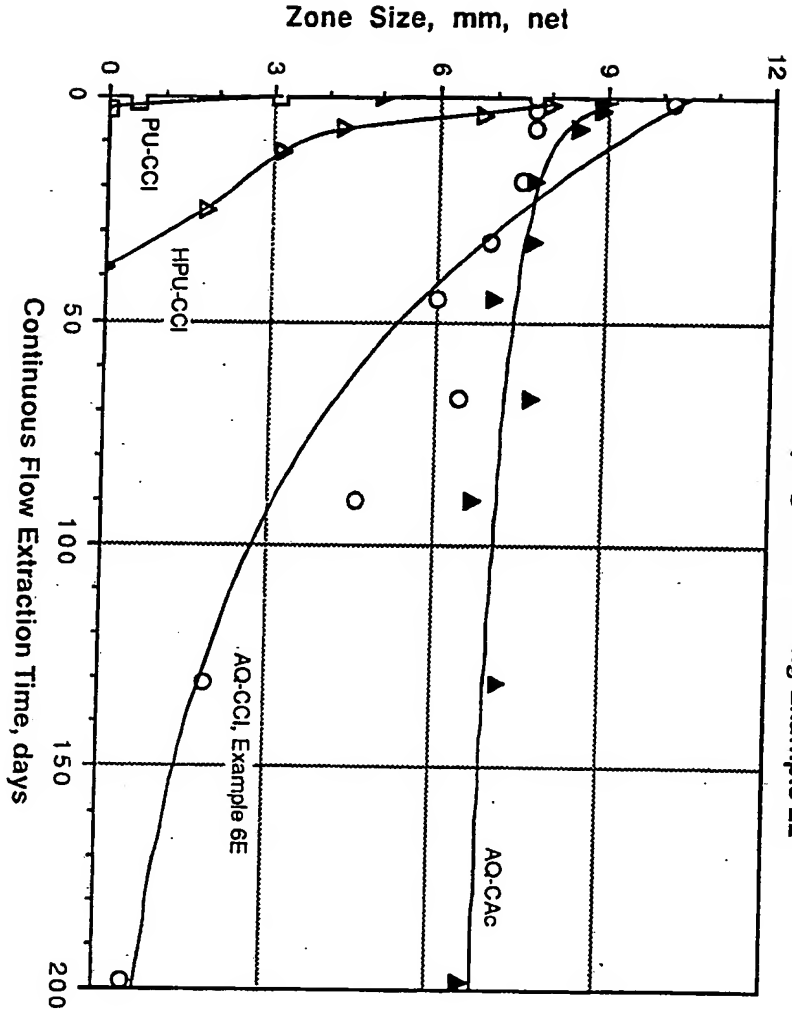

FIGURE 2

Chlorhexidine Impregnated Tubing-Example 22

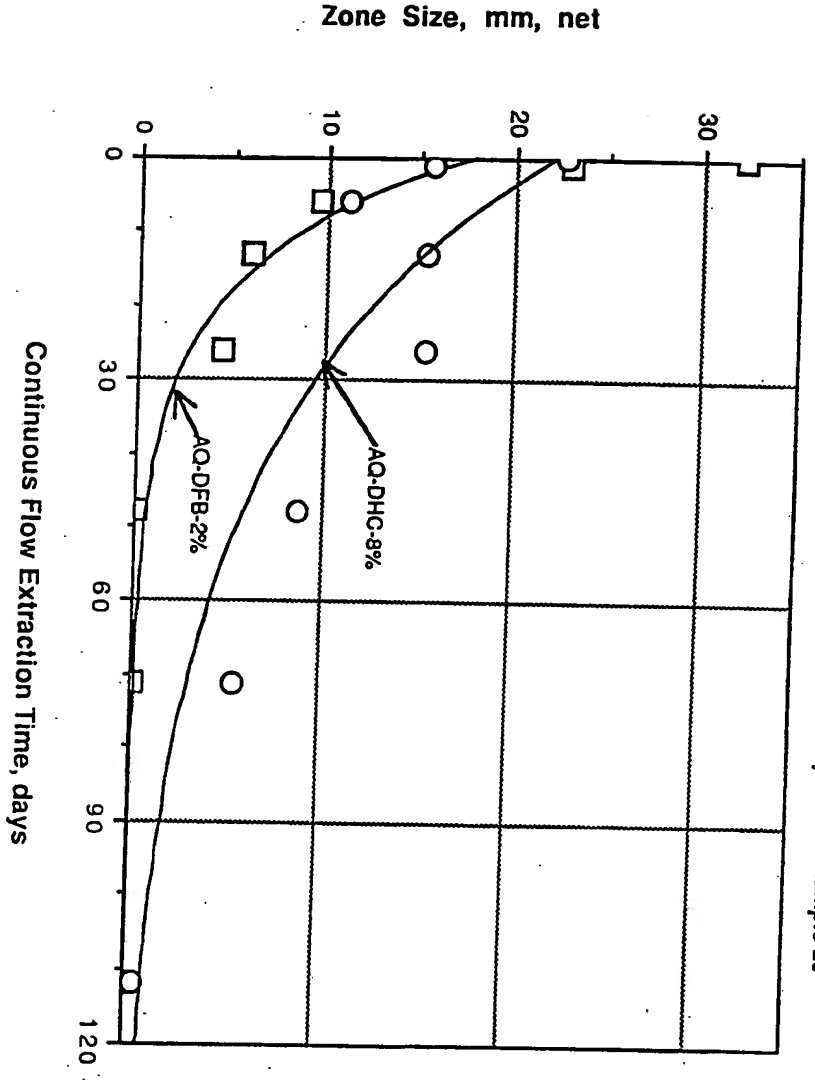

FIGURE 3
Activity of AQ Samples with Doxycycline Compounds-Example 20

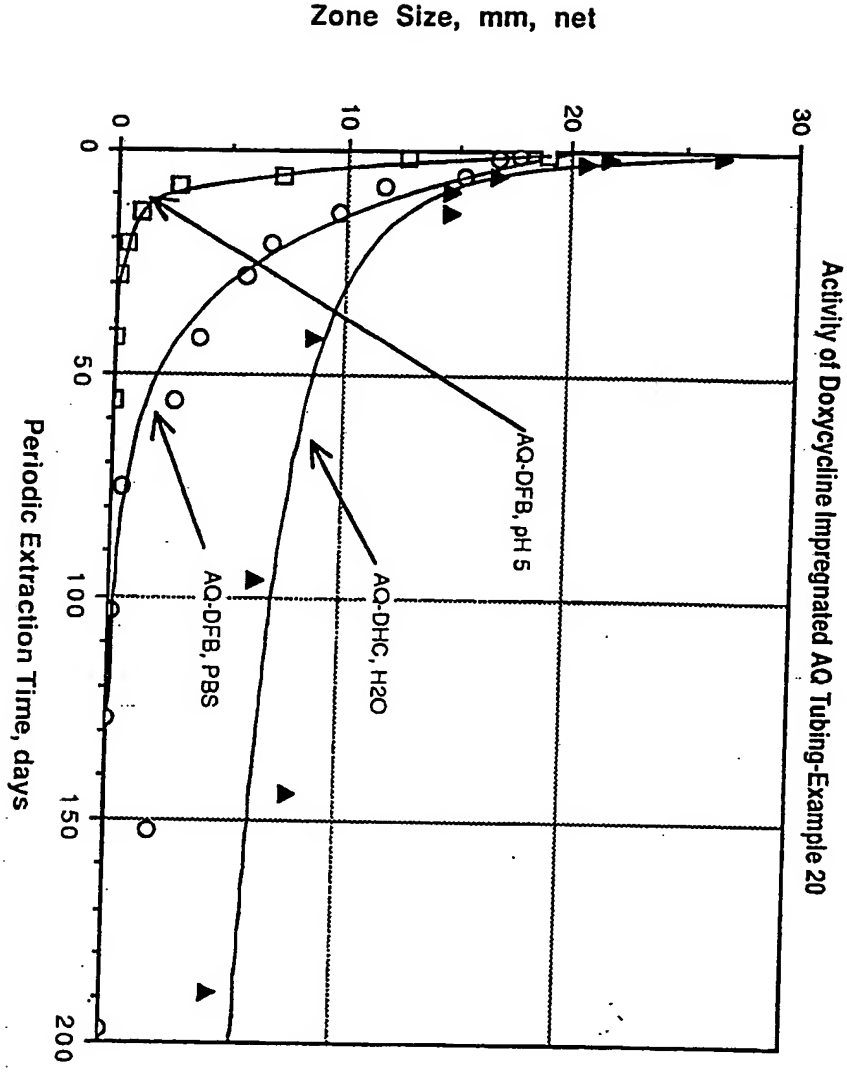
Zone Size, mm, net
0
10
20
30
0
50
100
150
200
Periodic Extraction Time, days
AQ-DFB, pH 5
AQ-DFB, PBS
AQ-DHC, H2O
Activity of Doxycycline Impregnated AQ Tubing-Example 20

FIGURE 4

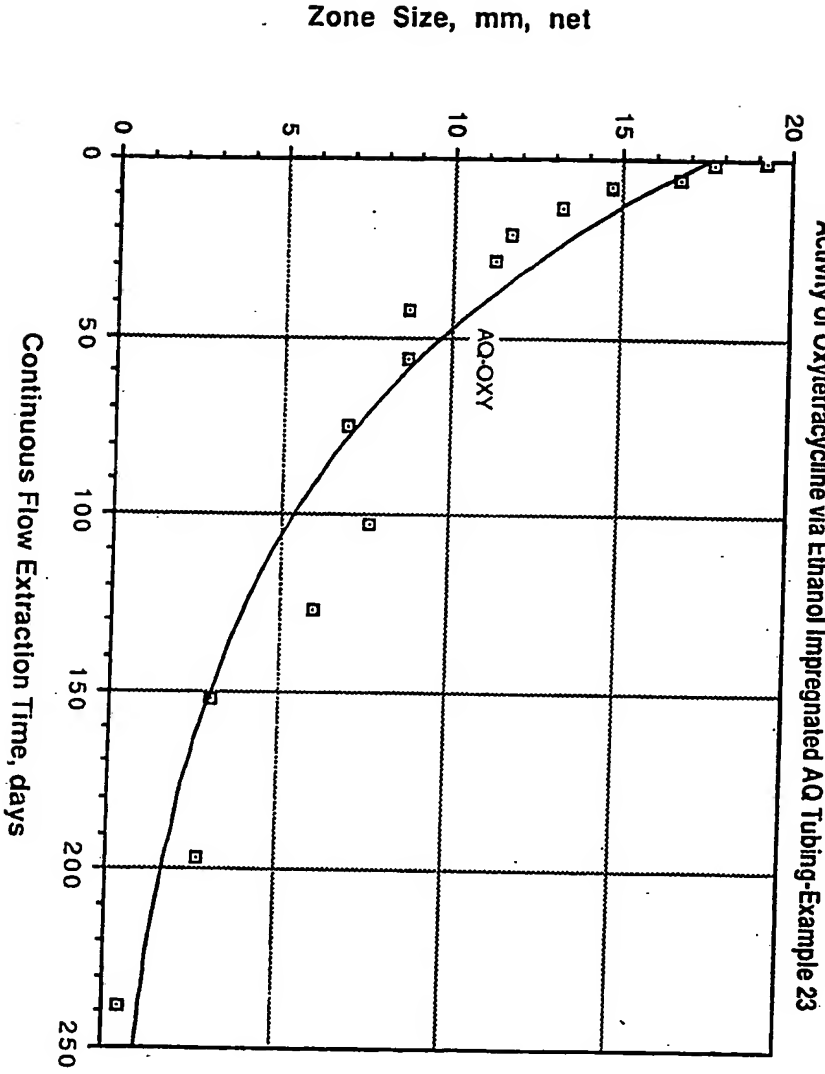
Zone Size, mm, net
0
5
10
15
20
0
50
100
150
200
250
Continuous Flow Extraction Time, days
AQ-OXY
Activity of Oxytetracycline via Ethanol Impregnated AQ Tubing-Example 23

FIGURE 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/08528

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61M 25/00
US CL :424/484; 604/264, 265
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/484; 604/264, 265; 424/422, 423, 424, 425, 433, 485, 486; 604/164

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPAT CANNULA#, POLYMER, SUSTAINED RELEASE.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,439,583 (GOULD ET AL) 27 MARCH 1984; Column 4, lines 6-23.	1-33
Y	US, A, 4,581,028 (FOX, JR. ET AL) 08 APRIL 1986; Column 6, lines 49 to Column 7, line 19.	1-33
Y	US, A, 4,917,686 (BAYSTON ET AL) 17 APRIL 1990; See entire document.	1-33

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
18 NOVEMBER 1992	21 DEC 1992
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer ROBERT H. HARRISON Telephone No. (703) 308-2351